

REMARKS

Claims 1-5, 8-11, and 31-37 are currently pending in this application. Claims 12-30 and 32, which were previously withdrawn, have been canceled in this Amendment.

Applicants wish to remind the Office of co-pending application Serial No. 09/816,467 and have attached a recent Office Action issued in that application, for convenience.

Claim Rejections

On pages 2-6 the Office maintained the rejection of claims 1-5, 8, 11, 31, 34, 36, and 37 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,780,024 ("the '024 patent), in view of Halpern et al., Infection and Immunity, (1990) vol 58, pp. 1004-09 ("Halpern"). Neither the '024 patent, nor Halpern, though, discloses a fusion protein that has "at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C," as claimed in independent claims 1 and 31. This deficiency was acknowledged by the Office on page 3 of the Office Action ("yet U.S. Patent No: 5780024 does not disclose, specifically, that the C-fragment should contain at least 11 amino acids of the B-fragment nor that there should be exactly 11 (claim 37).")

Despite the lack of a specific disclosure, the Office asserted that the '024 patent discloses

embodiments having 2 or 8 additional amino acids (col 6) and indicate that more or less [sic] are encompassed by the invention, and can be added, particularly as a matter of convenience in the cloning process e.g. col 6, lines 37-40. However, Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its [sic] probable that it is the addition of these amino acids of the B-fragment that

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results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a [sic] much greater portion the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the biding properties, e.g. the fragment used by Halpern contains an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007.

Office Action at p. 3. The Office then asserted that the claimed invention is obvious because

the skilled [artisan] would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the invention disclosed in U.S. Patent No: 5780024[.]

Id. But, the basis for this rejection amounts to an “obvious to try” standard, which the Federal Circuit has found to be inappropriate for evaluating obviousness under 35 U.S.C. § 103.

In *In re O’Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988), the Federal Circuit described one “obvious to try” scenario, which is not the proper scenario for determining obviousness, wherein “what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Id.* at 903, 7 U.S.P.Q.2d at 1681. The Office’s explanation that “at the time the instant invention was made, it would have been an obvious matter of routine

optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment," Office Action at p. 3, would be an attempt to try numerous possible choices of fragments until finding one which achieved the characteristics of the claimed fusion protein. But, the prior art cited by the Office does not provide any indication that any of these choices of fragments would achieve retrograde axonal or transynaptic transport. In contrast, the fusion protein recited in the claims, comprising "at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C," achieves these results, as demonstrated in Examples 7, 8, and Table 1 of the instant specification.

Furthermore, the Office did assert that the fusion protein disclosed in the '024 patent "is **expected** to undergo 'transynaptic transfer between neurons," Office Action at p.4 (emphasis added). But this is not actually disclosed or demonstrated and the Office has not explained the basis for this asserted "expectation." *Prima facie* obviousness requires more. Obviousness requires that the Office make findings of the person skilled in the art or the specific principle within the knowledge of the skilled artisan that would have motivated one with no knowledge of applicants' invention to make the combination in the manner claimed. *Teleflex v. KSR Int'l*, 119 Fed. Appx. 282, 285-86 (Fed.Cir. 2005) (unpublished) (citing *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." (emphasis added)) and *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) ("In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no

knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. (emphasis added)"). Here, there are no findings to support the alleged "expectation."

Thus, the basis for the rejection over the '024 patent and Halpern is that it was "obvious to try" the claimed parameters, without any indication that the claimed parameters would be successful. Because this basis is improper for a *prima facie* showing of obviousness under 35 U.S.C. § 103, Applicants respectfully request that the rejection of independent claim 1, and claims 2-5, 8-11, 32, 33, 36, and 37, which depend on claim 1, and of independent claim 31, and claims 34-37, which depend on claim 31, be withdrawn.

The Office rejected claims 9 and 10 under 35 U.S.C. § 103 as being unpatentable over the '024 patent in view of Halpern and further in view of Fishman et al., J. Neurological Sciences (1990) vol. 98, pp. 311-32 ("Fishman"). See Office Action at pp. 6-7. To make this rejection, the Office relied on "the motivation to add amino acids of the B-fragment as taught by Halpern et al., as discussed above." *Id.* at p. 6. Though the Office asserted that Fishman provides a reasonable expectation of success because it "teach[es] that the large size of such [multimeric] complexes does not interfere with the uptake of the complexes into neurons . . . ," Fishman also fails to demonstrate that a fusion protein comprising "at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C" will achieve retrograde axonal and transynaptic transport. Thus, the Office is forced to rely on an invitation to experiment with different combinations of fusion protein members to achieve the results demonstrated by the claimed fusion protein. Because "obvious to

try” is not the correct standard for obviousness under 35 U.S.C. § 103, Applicants respectfully request that the rejection be withdrawn.

On pages 7-8 of the Office Action, the Office rejected claims 1-5, 8, 11, 31, and 33-36 under 35 U.S.C. § 103 as being unpatentable over the '024 patent in view of Halpern and further in view of U.S. Patent No. 6,159,948 (“the '948 patent”). The Office asserted that the '948 patent provides motivation to deliver the SMN protein to the central nervous system. The '948 patent, though, does not teach using “at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C.” Therefore, one of skill in the art would not find that the combination of the '024 patent, Halpern, and the '948 patent disclose that a fusion protein with at least 11 amino acids of fragment B can achieve achieve the retrograde axonal and transynaptic transport demonstrated by the claimed fusion proteins. Accordingly, Applicants respectfully request that the rejection be withdrawn.

On pages 8-10 of the Office Action, the Office also asserted that claims 1-5, 8, 11, 31, 34, and 36 are unpatentable under 35 U.S.C. § 103 over Francis et al., J. Biol.Chem., (1995) vol. 270, pp. 15434-42 (“Francis”) in view of Halpern. The Office acknowledged that “Francis et al. do not disclose, specifically that the C-fragment should contain at least 11 amino acids of the B-fragment.” Office Action at p. 9. Again, though, the Office relies on the “obvious to try” argument, commenting

the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment(as

taught by Halpern) when practicing the method taught and proposed by Francis et al.

Id. What the Office characterizes as “routine optimization” is not routine optimization at all. It is merely an attempt to relabel the “obvious to try” standard, which is inappropriate for assessing unpatentability under 35 U.S.C. § 103 when the examples of the instant specification demonstrate that the claimed fusion protein can achieve retrograde axonal and transynaptic transport. This feature is not demonstrated in any prior art. Thus, in the “routine optimization” of Halpern’s work, one would be surprised to obtain the effects Applicants discovered. Accordingly, Applicants respectfully request that the rejection over Francis in view of Halpern be withdrawn.

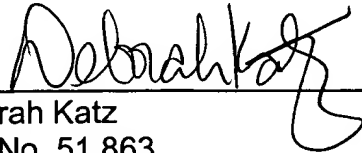
Finally, on pages 10-11, the Office rejected claims 8, 11, 31, 33, 35, and 36 under 35 U.S.C. § 103 as being unpatentable over Francis in view of Halpern and further in view of the ‘948 patent. Though the Office asserted that the ‘948 patent teaches the SMN protein fused to tetanus toxin, the ‘948 patent does not disclose a fusion protein with “at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C.” Therefore, Francis taken in view of Halpern and the ‘948 patent does not render the claimed invention obvious and Applicants respectfully request that the rejection be withdrawn.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 12, 2006

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Attachment: Copy of Office Action for co-pending application Serial No. 09/816,467.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,467	03/26/2001	Laurent Coen	3495.0174-01	7062
22852	7590	12/29/2005		
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413				
			EXAMINER CHEN, SHIN LIN	
			ART UNIT 1632	PAPER NUMBER

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
JAN 03 2006

Docketed 61-03-06 Attorney KJM/DVK
Case 3495.0174-01
Due Date 03-29-06 w/ep to
Action resp
By pmk

Office Action Summary



Application No.

007816,467

Examiner

Shin-Lin Chen

Applicant(s)

COEN ET AL.

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17, 18, 21-23, 34 and 35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17, 18, 21-23, 34 and 35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |



Application/Control Number: 09/816,467
Art Unit: 1632

Page 1

DETAILED ACTION

In response to the "Decision on Appeal" mailed 10-26-05, the finality of the Official action mailed 6-4-03 has been withdrawn. In view of a new art rejection, an action on merit follows.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "SMN", "NT-3", "NT-4/5", "CRE" and "ICE" in claim 22 are vague and renders the claim indefinite. These terms are abbreviations and can stand for various meanings. Spelling out the terms at the first occurrence would be remedial.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Art Unit: 1632

4. Claims 17 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Fairweather et al., 1995 (US Patent 5,443,966).

Claims 17 and 21 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment.

Fairweather teaches construction of expression plasmid pTet18 expressing a polypeptide which comprises 121 residues of B fragment and all 451 carboxy-terminal residues of C fragment of tetanus toxin, transfection of *E. coli* cells with said expression plasmid, and culturing of the transfected *E. coli* cells. Fairweather assays expressed tetanus hybrid protein by SDS-PAGE gel and Western blotting using rabbit anti-C fragment sera (e.g. column 8). Since the specification fails to specifically define the term "active molecule", therefore, the solution containing the expressed tetanus hybrid protein during the assay is considered an active molecule. Further, claims 17 and 21 are product claims and Fairweather teaches every limitation of the claimed product. Thus, it is inherent that the tetanus hybrid protein taught by Fairweather has the ability to transfer in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse. Therefore, claims 17 and 21 are anticipated by Fairweather.

5. Claims 17 and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705).

Claims 17 and 21 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons. Since the specification fails to specifically define the term "active molecule", therefore, the solution containing the TTX is considered an active molecule. Further, the claimed hybrid fragment of tetanus toxin encompasses full-length tetanus toxin protein. Thus, claims 17 and 21 are anticipated by Fishman.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1632

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 17, 18, 21, 23, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) in view of Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) and Hohne-Zell et al., 1993 (FEBS Letters, Vol. 336, No. 1, p. 175-180).

Claims 17, 18, 21, 23, 34 and 35 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues or further containing fragment A devoid of its zinc-binding motif, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment. Claims 23, 34 and 35 specify the active molecule is a polynucleotide encoding a protein and said polynucleotide further comprises a promoter capable of expression in neurons or further comprises an enhancer.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is

Art Unit: 1632

superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons (last 4 lines).

Fishman does not teach a hybrid fragment of tetanus toxin in association with a polynucleotide under the control of a promoter and/or an enhancer. Fishman also does not specifically teach a hybrid fragment further comprising a fraction of a fragment A devoid of its toxic activity corresponding to zinc-binding motif between amino acid residues 225 and 245.

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo, and the foreign gene can be specifically controlled by the gene's promoter. The toxic portion of the protein resides in the amino terminal (e.g. p. 3 and 4). The non-toxic portion of tetanus toxin (C fragment) can be covalently attached to polylysine whose positive charge serves as a bridge to the non-covalent, electrostatic binding of the negatively charged DNA (e.g. p. 4). Mueller lists neuronal cells that can be used for gene delivery in vitro (see Table 1). Mueller also teaches using RSV promoter for neuron-specific expression of beta-galactosidase (e.g. p. 9).

Hohne-Zell teaches zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain and replacement of histidine (position 233) by cysteine or valine and of glutamate (position 234) by glutamine completely abolished the activity of light chain on calcium induced catecholamine release (e.g. abstract).

Art Unit: 1632

It would have been obvious for one of ordinary skill at the time of the invention to generate claimed hybrid fragment or composition because modifying the composition of Fishman et al. by replacing the polypeptide with a larger fragment of tetanus toxin (in addition to C fragment) was better in delivering a molecule to neurons and also because C-fragment of the tetanus toxin alone is not toxic and the toxic portion of the protein resides in the amino terminal, and in combination with the teaching of Hohne-Zell that the putative zinc-binding domain constitutes the active site of the tetanus toxin light chain would make it obvious for one of ordinary skill to remove said zinc-binding domain when generating a tetanus toxin fragment for neuron specific transport. It also would have been obvious for one of ordinary skill at the time of the invention to associate the tetanus protein as taught by Fishman with a polynucleotide because Fishman teaches that atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons, and Mueller teaches that the tetanus C-fragment can be used to complex with DNA for neuron specific gene transfer in vivo and use of RSV promoter for said gene transfer.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a tetanus hybrid protein capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller and Fishman with reasonable expectation of success.

9. Claims 17, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) in view of

Art Unit: 1632

Khan et al., 1995 (WO 95/04151) and Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15).

Claims 17, 21 and 22 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment. Claim 22 specifies the active molecule is a protein as recited.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons (last 4 lines).

Fishman does not specifically teach association of the recited proteins with the claimed hybrid fragment of tetanus toxin.

Khan teaches construction of a DNA construct comprising a DNA sequence encoding a fusion protein of the formula: TetC-(Z)a-Het, wherein the TetC is the C fragment of tetanus toxin and Het is a heterozygous protein (e.g. abstract). Khan teaches using the DNA construct in producing a fusion protein and the use of said fusion protein as a vaccine (e.g. p. 4).

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo. The non-toxic portion of tetanus toxin (C fragment) can be covalently attached to polylysine whose positive charge serves as a bridge to the non-covalent, electrostatic binding of the negatively charged DNA (e.g. p. 4). Mueller lists neuronal cells that can be used for gene delivery in vitro (see Table 1). Mueller also teaches using RSV promoter for neuron-specific expression of beta-galactosidase (e.g. p. 9).

It would have been obvious for one of ordinary skill in the art at the time of the invention to associate the recited proteins in claim 22 with the claimed hybrid fragment of tetanus toxin because Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons and Khan teaches association of the C fragment of tetanus toxin with any heterozygous protein, and further, most of the proteins recited in claim 22 are expressed in neurons and Mueller teaches using the C-fragment as a carrier molecule for neuron specific gene transfer.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to deliver the protein as a vaccine as taught by Khan or deliver the therapeutic protein to neurons as taught by Mueller and Fishman with reasonable expectation of success.

Conclusion

No claim is allowed.

Art Unit: 1632

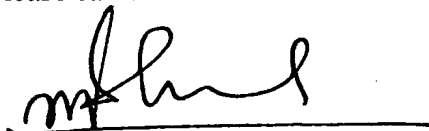
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

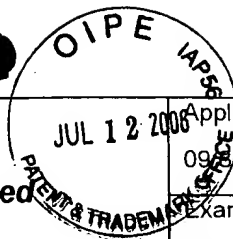
Shin-Lin Chen, Ph.D.



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SHIN-LIN CHEN
PRIMARY EXAMINER

**Notice of References Cited**

Application/Control No.

092816,467

Applicant(s)/Patent Under
Reexamination
COEN ET AL.

Examiner

Shin-Lin Chen

Art Unit

1632

Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,443,966	08-1995	Fairweather et al.	435/69.3
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 95/04151	02-1995	WIPO	Khan et al.	
	O					
	P					
	Q					
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	T					

NON-PATENT DOCUMENTS

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	U	Fishman et al., 1996, Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705.
	V	
	W	
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